DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	12/05/2023-12/11/2023* FEI NUMBER 3012740315

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Dr. Sushil Jaiswal, Executive Director Quality

FIRM NAME	STREET ADDRESS
Torrent Pharmaceuticals Limited	Unit - 2, 105 106 119 Survey No 102
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Chhatral, Gujarat, 382729 India	Drug Product Manufacturer (OSD Oncology)

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

QUALITY SYSTEM
OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, the quality unit failed to investigate deviations and investigations thoroughly that could potentially impact the patient safety and product quality. For example:

The firm's QC found failing results for (b) (4) Capsules (b) (4) mg Batch #(b) (4) (US/EU Market Exhibit Batch) **(OOS/N/FP/22/006)** for Assay test ((b) (4) %) and (b) (4) Uniformity test ((b) (4) %) with Acceptance Criteria of NLT (b) (4) % and NMT (b) (4) for Assay and (b) (4) for the US market, while co-testing Batch #(b) (4). You attributed the root cause to dilution error where the analyst used the wrong pipette for final sample dilution as vice-versa (i.e. For (b) (4) test (b) ml pipette used instead of (b) ml pipette and for Assay test (b) ml pipette used instead of (b) ml pipette).

However, the pipettes to be used by analyst for Assay and (b) (4) tests are not described in STP #IPT/2220 Ver. 00 ((b) (4) *Capsules* (b) (4) / (b) (4) / (b) (4) *mg,* 04/29/2022 effective date) which has been utilized to test all exhibit batches. Re-analysis was performed using the same solutions of assay and (b) (4) uniformity for Batch #(b) (4) after re-dilution from same stock in (b) (4) set. You obtained the first passing results and invalidated the initial OOS results without scientific justification. You also failed to take appropriate actions (CAPA) in the investigation to address the root cause such as revising the STP which was utilized for testing both strengths of (b) (4) Capsules.

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OBSERVATION 2

The responsibilities and procedures applicable to the quality unit are not in writing and fully followed for your formulation manufacturing operations. Specifically,

A. You failed to perform a performance qualification (PQ) for the (b) (4) tester (ID #TPL-QC-149) located in the Packing Material Test (Room #(b) (4)) and released the equipment for use on February 04, 2020.

In addition, you failed to prepare a qualification protocol and report for the qualification of the equipment as required per your Validation Master Plan (VMP/BI/ONC/01) and you failed to include the equipment in a calibration program as required by SOP#BIQC-088-01 (*Operation and Cleaning of*(b) (4) *Tester,* February 20, 2020 effective date). The equipment was utilized to perform aluminum foil testing utilized in blister packaging for the following (b) (4) Capsules ((b) (4) #(b) (4)) exhibit batches listed below.

Sr. No	Product name	Strength	Batch No	Material Code	Batch Type	Material Name	A.R. No.	Date of Testing
1	(b) (4) Capsule	(b) mg	(b) (4)	(b) (4)	Exhibit	(b) (4) ALUMINIUM FOIL WITH (b)	ARDN8J0019	28.03.22
				(b) (4)	Exhibit	(b) Foil (b) mm (b) (4)	ARDN8J0015	22.03.22
2	(b) (4) Capsule	(b) mg	(b) (4)	(b) (4)	Exhibit	(b) (4) mm (b) (4) ALUMINIUM FOIL WITH (b)	ARDN8J0019	28.03.22
				(b) (4)	Exhibit	(b) Foil (b) mm (b) (4)	ARDN8J0015	22.03.22

B. When counting microbial plates for colonies (CFU/mL) in your Microbiological Lab, a calculation is performed to determine the CFU/ml results where you take the (b) (4) and (b) (4) of sample taken. You state in the Test Data Sheet under "Note" (in Logbook #BIQC-007-T01-

01-230) "If the result is fraction, round the nearest whole number for reporting final result." However, you have not established a procedure in the microbiology lab for "calculating of result: CFU/mL" and rounding numbers and/or significant figures. Your SME (Assistant Manager of QC-Microbiology) stated the calculation formula for "CFU/mL" was taken from USP General Chapter <61> (*Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*) prior to 2013 version. However, the calculation formula is not referenced in the provided USP General Chapter <61>.

In addition, I observed in the "General Test Data Sheet for Microbial Enumeration Test and Test for Specified Microorganisms (Microbial Limit Test)" for (b) (4) Capsules (b) (4) mg (b) (4) s Alu Alu Blister Pack for Batch #(b) (4) that a calculation formula is given to calculate Total Microbial Count for Total Aerobic Microbial Count (TAMC) and TYMC (Total Yeast & Mold Count) as (b) (4) (Volume of Test Sample, unit of measure is not provided). The referenced calculation is not referenced in the SOP and in the USP General Chapter <61> (*Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*, prior to 2013 version).

For example, you observed 21 counts on December 4, 2023 for sample ID #(b) (4) ((b) (4) (b) (4) sample) and you reported "(b) (4)" under "Observe count CFU/mL" after performing the calculation. When asked your Assistant Manager QC-Micro to perform the calculation, I observed the result was "(b) (4)", but your analyst rounded the reported result to "(b) (4)" without any justification.

Sample ID#	Observed Count	Volume of Sample Taken	Calculation of Result (CFU/mL) = Observed / Volume of Samples Taken
(b) (4)	21	(b)	(b) (4) Firm reported "(b)" CFU/mL

In addition, you do not maintain a usage and/or maintenance logbook for the colony counters (ID #TPL-QC-008 and TPL-QC-039). (b) (4) Capsules ((b) (4) #(b) (4)) require microbial testing. For total aerobic microbial count (TAMC), microbiological quality (total combined yeasts/ molds count, and Escherichia Coli).

C. You have not performed (b) (4) integrity testing for holes and leaks for the (b) (4) utilized in the (b) (4) /RABS in Dispensing (ID #TPL-WH-003) and (b) (4) (ID #TPL-ON-020) of raw materials utilized for (b) (4) Capsules ((b) (4) #(b) (4)) exhibit batches.

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D. You do not document and investigate critical alarms in your manufacturing batch records or including alarm reports as part of the batch manufacturing records for (b) (4) /RABS in Dispensing (ID #TPL-WH-003) and (b) (4) (ID #TPL-ON-020) operations utilized for (b) (4) Capsules ((b) (4) #(b) (4)) exhibit batches. In addition, these are alarms are kept in the software for only (b) (4) .

FACILIITES AND EQUIPMENT SYSTEM
OBSERVATION 3

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent malfunctions, contamination, that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,

A. You have not performed a cleaning validation for the glassware washer (Smeg Model #GW3060S, ID #TPL-QC-020) located in the Microbiology Lab and verified the effectiveness of the manual cleaning of glassware that cannot fit into the glassware washer to ensure they are cleaned. In addition, SOP #BIMC-045-01 (*Operation and Cleaning of Glassware Washing Machine*) does not state the cleaning agents to be utilized for the glassware washing machine.

B. You failed to appropriate clean and maintain (b) (4) incubator (ID #TPL-QC-010), which is utilized to incubate microbial plates for (b) (4) -(b) (4) ^{0} C storage conditions in your Microbiology Lab. On December 8, 2023 during my inspectional walkthrough of the area, I observed presence of mildew, rust, and buildup of unknown dirt/dust on the floor and walls inside the (b) (4) incubator. According to Incubator Usage Record logbook #BIMC-014-F01-207, the incubator was last cleaned on November 28, 2023 and the cleaning frequency is (b) (4) .

The following 34 plates were observed being incubating inside the (b) (4) incubator:

Incubation Date	Sample Details/Purpose	Batch #/AR #/Reference
12/05/2023	EM of Micro Lab	(b) (4)
12/05/2023	MLT Analysis (b) (4)	
12/06/2023	EM of Micro Lab	
12/07/2023	EM of Micro Lab	
12/08/2023	EM of Micro Lab	

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(b) (4)

C. Several capped plastic bottles with condensation were observed in Glassware Washing (Room #FG047) on December 8, 2023. According to your Assistant Manager, QC-Micro, these bottles are cleaned and ready for use for (b) (4) sampling collection.

D. Worn gaskets were observed on December 5, 2023 inside the (b) (4) Capsule filling machine (ID #TPL-ON-012) located in Capsulation Room #(b) (4).

PRODUCTION SYSTEM

OBSERVATION 4

Components for drug product manufacturing are not weighed and measured. Specifically, you have not defined and recorded the amount (either by weight or volume) of (b) (4) solution required for (b) (4) (b) (4) for (b) (4) Capsules (b) (4) mg/(b) (4) mg in the batch manufacturing records at Step (b) (4) ((b) (4) (b) (4) Process Parameters (Lot-(b)). According to your Executive Director of Operations, (b) (4) solution is a critical component in the (b) (4) Capsules ((b) (4) #(b) (4)) manufacturing process.

I observed on December 8, 2023 during the manufacturing run of (b) (4) for (b) (4) Capsules (b) (4) mg, Batch #(b) (4), and reviewing of exhibit batch records for Batch #(b) (4) – (b) (4) ((b) (4) mg) and (b) (4) – (b) (4) ((b) (4) mg) that you utilized a vessel of solution preparation (ID #TPL-ON-018) filled with (b) (4) solution to be used during the (b) (4) solution stage. However, the amount of the (b) (4) solution required is not listed and recorded in the batch manufacturing record (Form #FN.011.02-20.709E).

LABORATORY CONTROL SYSTEM

OBSERVATION 5

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established.

Specifically, accuracy, sensitivity, specificity, and reproducibility of (b) (4) uniformity sample preparation and testing has not been established.

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According to Protocol #VF-BL-F-0029-00 and Report #VR-BL-F-0029-00 (*Assay by HPLC*), you have not performed any method validation, method verification, and/or method suitability studies for (b) (4) uniformity (b) (4) by HPLC to verify if the method is suitable for the intended use.

In addition, you have not fully validated and/or verified STP #AM/4955/04 (*Analytical Test Method for* (b) (4) *Capsules* (b) (4), (b) (4), *and* (b) (4) *mg*) for assay and degradation products test received from your R&D. It states in Section 2 of STP #AM/4955/04 (Assay by HPLC) that water ((b) (4) is to be utilized. However, (b) (4) water is not captured in STP #IPT/2220 (*In Process Standard Test Procedure for* (b) (4) *Capsules /* (b) (4) *Capsules*).

***DATES OF INSPECTION**

12/05/2023 (Tue), 12/06/2023 (Wed), 12/07/2023 (Thu), 12/08/2023 (Fri), 12/11/2023 (Mon).

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